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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
G01N 30/88, B01L 3/00

A1

(11) International Publication Number: WO 93/17328

(43) International Publication Date: 2 September 1993 (02.09.93)

(21) International Application Number: PCT/GB93/00339

(22) International Filing Date: 18 February 1993 (18.02.93)

(30) Priority data:
92301405.4 20 February 1992 (20.02.92) EP
(34) Countries for which the regional or international application was filed: GB et al.

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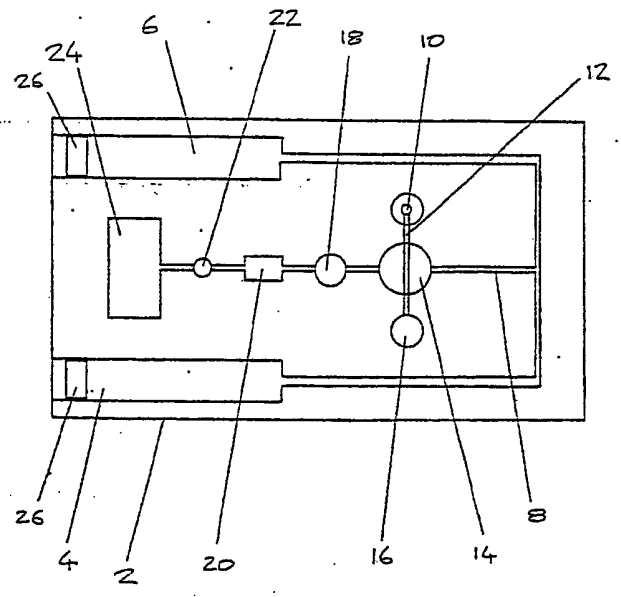
(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: LIQUID CHROMATOGRAPHY APPARATUS



(57) Abstract

In a liquid chromatography apparatus comprising a reusable reader device for use with disposable chromatography cassettes, each cassette has a capillary (12) for drawing a sample into a valve (14) located between a mixing apparatus (4, 6) and the chromatography separation means (20). The valve has a predetermined internal volume such that on rotation a sample of fixed quantity is placed in line between the separation means (20) and the mixing apparatus (4, 6). The mixing apparatus has elongate chambers (4, 6) with moveable plugs (26) pushed by piston rams of the reader device to provide a combined flow of varying relative concentration. Alternatively, it has resiliently flexible elongate chambers (4, 6) of varying cross-section. When the cassette is inserted into the reader, rollers squeeze the chambers (4, 6) to provide the combined flow. The reader has a pulsed xenon tube and two photodetectors, one for measuring attenuation of sample fractions exiting the separation means (20) and the other the intensity of the light source, the difference between the two yielding the measurement.

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LIQUID CHROMATOGRAPHY APPARATUS

The present invention relates to a liquid chromatography apparatus and more particularly to a liquid chromatography apparatus of reduced overall dimensions.

Known chromatographic systems, for instance for use in the separation of haemoglobin fractions, comprise a column containing a substrate or packing material onto which a sample is loaded. A liquid stream of buffer solution, often of varying concentration, is passed through the column to separate the various fractions within the sample. Particular fractions of the sample break away from the substrate at particular concentrations of the buffer and, hence, by varying the concentration which passes through the column and monitoring the quantity of sample leaving the column, the proportions of various fractions within the sample may be measured.

Typically the devices have been of the high pressure type using columns of about a 20cms in length with high pressure pumps to conduct the elution at pressures of 1000-2000 psi. More recently, however, a device has been proposed using a column of smaller size which works at lower pressure and is of a size suitable for "desk-top" use.

Normally the concentration of the buffer stream is varied by using two (or more) pumps and controlling them to deliver two (or more) different concentration buffers at a combined constant or varying flow rate and with varying proportions.

An alternative to using two pumps is to use a single pump with a proportioning valve on the intake side which can be controlled to achieve the same effect.

It is an object of the present invention to provide a liquid chromatography device of greatly reduced size, such that it may preferably be hand held.

It is a further object to provide an apparatus of reduced size which may deliver fluids at a combined constant flow rate or suitably varying flow rate and at varying proportions.

It is a further object to provide, on a sample analysis apparatus, means of reduced size to introduce a sample into the apparatus.

According to the present invention there is provided a hand-held chromatography device comprising a reader device and a chromatography cassette for separating, with a varying concentration buffer, fractions of a sample on a binding material and determining the relative quantities of the fractions in the sample, said chromatography cassette being mountable with said reader device and comprising:

a chromatography separation means containing a binding material for binding a sample;

a sample induction means connected to said chromatography separation means for providing a sample, supplied by a user, to said chromatography separation means;

a mixing apparatus connected to said chromatography separation means for producing a flow of varying concentration buffer therethrough; and

a detection path downstream of said chromatography separation means at which the flow of a fraction of said sample out of said chromatography separation means can be detected;

said reader device being mountable with one of a plurality of interchangeable chromatography cassettes and having measurement means for measuring quantities of a sample flowing through said detection path and at least one of means to display and means to store information relating to the results of the detection.

Hence, with the present invention, it is possible to have a selection of small and completely self contained cassettes, each containing the necessary fluids and materials for a particular test. The reading device comprises the expensive easily reusable parts (e.g. means for measurement, calculation and display) of the total apparatus and the previously awkward use of differing

quantities of materials in a fixed apparatus is avoided by providing a self contained disposable cassette. Depending on cost and suitability, the actual detector of the system may be part of either the cassette or the reader. Thus the detector could be a photo detector and light source on the reader or a detector on the cassette, e.g. an electrode for detecting redox potential, connectable to analysis circuitry in the reader and disposable with the cassette.

Preferably, the mixing apparatus comprises a plurality of elongate chambers, each holding a fluid, each being connected at one end to a common path leading to said chromatography separation means, each being open at the other end, and each having a respective plug sealing with the inner surface of a respective elongate chamber so as to hold fluid within the respective elongate chamber, each plug being moveable lengthwise of the respective elongate chamber so as to expel, into the common path, the respective fluids from the respective elongate chamber. Additionally, the reader device may comprise respective piston rams for moving said plugs, the rates of extension of said piston rams in use being controlled by said reader device so as to control the rates at which fluid is expelled from respective elongate chambers.

This provides a very simple way of producing fluid flow, the relative concentration of which may be easily varied by varying the extension rates of the piston

rams. Further variation may be provided by using elongate chambers of differing cross-sectional areas.

Alternatively, the mixing apparatus comprises a plurality of resiliently flexible elongate chambers, each holding a fluid, each being connected at one end to a common path leading to said chromatography separation means and each having a cross-section which varies along the length of the elongate chamber, such that, in use simultaneously a compression may be formed in each elongate chamber to reduce the cross-section of that elongate chamber and said compressions may be moved towards respective said one ends so as to expel, into the common path, the respective fluids from the elongate chambers, at rates determined by the cross-sectional area of each elongate chamber.

This provides a very simple way of producing a varying relative concentration flow which unlike known variable pumps or controllable valves which are bulky and prohibitively expensive, may be easily incorporated in a disposable cassette. Preferably the reader device is such that the action of mounting the reader device with one of said chromatography cassettes, primes a mechanism to provide and move said compressions. Hence, the device reader provides a simple pump which may easily operate the cassette to produce the buffer flow. In contrast, the use of a known variable pump would require fluid connection

between the reader device and the cassette, thus making the apparatus more expensive and less reliable.

Preferably, the sample induction means comprises an inlet tube of sufficiently small cross-section to draw by capillary action, directly into a portion of the chromatography cassette a quantity of a sample fluid.

This provides a simple way of automatically drawing in a sample without use of any external power, an undesirable feature for a disposable unit.

Preferably the sample induction means comprises a sample valve having an aperture therein and being moveable between first and second positions such that, in use, in the first position, a sample fluid may pass through said valve so as to fill the length of the aperture and then, the valve may be moved to the second position so as to provide a sample of known quantity to said chromatography separation means. Hence a sample of a fixed quantity may be introduced into the cassette easily and without any special skill of the user. Further, the action of mounting the reader device with one of said chromatography cassettes preferably operates a valve mechanism so as to move the valve to said second position and hence no external power is required.

Preferably the sample induction means is internally coated with at least two compounds for mixing with the sample. This allows facilitated induction of the

sample and avoids a common requirement of known devices to mix the sample with these compounds prior to insertion. When for use with a sample of blood, preferably the compounds may comprise a compound to prevent blood from clotting and possibly a second or additional material to perform other needed initial sample preparation prior to full analysis, for instance, a mild acid for reducing the pH value of the sample in order to facilitate removal of the labile fraction of haemoglobin.

Preferably the chromatographic cassette further comprises a reservoir, preferably of absorbent material such as sponge, to absorb the fluid passing out from the chromatography separation means and the detection path.

Preferably said measurement means comprises a pulsed xenon tube light source and a photodetector for measuring attenuation due to out flow of sample fractions from said chromatography separation means. Hence power consumption of the light source may be greatly reduced over that of a tungsten filament lamp. Additionally, by using a further photodetector for measuring the intensity of the light source, readings may be obtained from the difference of the outputs of the two photodetectors and hence, susceptibility to inaccurate measurement due to variations in intensity may be alleviated.

According to a further aspect of the present invention, there is provided a mixing apparatus for mixing

a plurality of fluids to a varying relative concentration, said apparatus comprising a plurality of resiliently flexible elongate chambers each holding one of said fluids, each being connected at one end to a common path, and each having a cross-section which varies along the length of the elongate chamber, such that, in use, simultaneously a compression may be formed in each elongate chamber to reduce the cross-section of that elongate chamber and said compressions may be moved towards respective said one ends so as to expel, into the common path, the respective fluids form the elongate chambers at rates determined by the cross-sectional area of each elongate chamber.

Hence, this provides a very simple way of providing a varying relative concentration flow and unlike previous "desk-top" devices, no variable pumps or controllable valves are required. Preferably, the elongate chambers are arranged such that one or more rollers merely simultaneously produce the compressions, thereby requiring only a simple mechanism to produce the mixing operation.

According to another aspect of the present invention there is provided a sample analysis apparatus having a sample induction means comprising an inlet tube of sufficiently small cross-section to draw by capillary action, directly into a portion of the sample analysis apparatus a quantity of a sample fluid.

This provides a simple way of automatically drawing in a sample without the use of a pump or any external power.

The invention will be more clearly understood from the following description, given by way of example only with reference to the accompanying drawings in which:

Figure 1 illustrates an embodiment of a cassette of the chromatography apparatus of the present invention,

Figure 2 illustrates diagrammatically tubes of a mixing apparatus embodying the present invention,

Figures 3 (a) and (b) illustrates a sample inlet according to one embodiment of the present invention in load and run positions respectively,

Figure 4 illustrates an alternative embodiment of a cassette of the chromatography apparatus of the present invention.

The present invention relates to a liquid chromatography apparatus which comprises two parts, on the first hand a battery powered hand-held reader device which includes a microprocessor to control the elution and reading and to perform the analysis of the reading and a display to display or store or print-out and/or store the results, and on the other hand one or more interchangeable cassettes to be fitted to the reader for performing a particular test and which comprise all of the liquid paths

which would be contaminated by the sample and/or reagents. The cassettes each contain the necessary buffer fluids for the test and have means for accepting a sample prior to insertion of the cassette into the reader. Further, control cassettes may be provided to test the reader device, such control cassettes containing a sample of known composition. No liquid flow between the cassette and the reader is necessary since all the liquid paths are on the cassette and the reader causes the cassette to pump the fluid through its system such that the reader may detect quantities of flow through a window in the cassette.

Figure 1 illustrates a cassette, preferably of comparable size to common audio cassettes, for use with the hand held liquid chromatography system. The cassette as illustrated has a support structure 2 on which three flexible elongate chambers 4, 5, 6 containing the reagents required for the chromatography process are mounted. However, it will be appreciated that a cassette could comprise only two elongate chambers or more than three chambers depending on the mixture required.

As illustrated in Figure 2, the internal cross-sectional areas of the elongate chambers can be carefully chosen such that if they are squeezed, e.g. by a roller, simultaneously along their lengths, the fluids are expelled from each chamber at varying rates depending where the roller is along their length and they mix at junction 7 to

produce a mixture at constant flow rate whose concentration depends on the relative proportions of the fluids which is dependent on the cross-section of the chambers. Alternatively the cross-section of the chambers may be chosen so as to produce a mixture of varying flow rate. Each chamber may comprise a series of shorter chambers of differing internal cross-sectional areas or a single chamber of varying internal cross-sectional area. Although tubes having varying internal diameters may be used, it is preferred that the chambers are pre-moulded as blisters on or fixed to the surface of the cassette. Ideally, the chambers are of approximately semi-circular cross-section such that their lower surface lies in the plane of the surrounding surfaces of the cassette. In this case, the roller may easily expel the contained fluid.

Alternatively, as illustrated in Figure 4, the chambers 4,6 may be of constant cross-section, each having an open end and a plug 26 sealing with the chamber wall. The plugs 26 may be of rubber (possibly soft) such that they may be moved lengthwise of the chamber 4,6 to expel the contained fluids. Preferably, the plugs are moved by means of pistons/plungers of an associated reader which extend into the open ends of the chambers 4,6.

The flow from the two chambers 4,6 are combined in the common path 8 which leads to the sample introduction device illustrated in Figure 3.

The sample introduction device comprises a sample well 10 upon which the user may present, for instance, a finger prick of blood. A capillary passage 12 leads through a rotatable sample volume chamber 14 to a sample excess chamber 16. Hence, in use, the sample is drawn down from the sample well 10 by capillary action into the rotatable sample volume chamber 14 and finally into the sample excess chamber 16, forming a continuous volume through the chamber 14. The rotatable sample volume chamber may then be rotated so as to be in line with the common path 8. This rotation means that a predetermined volume of sample (length of the swivelling part times its cross-sectional area) is presented for loading onto the separation means 20 without the user having to measure the amount at all. As an alternative the sample volume chamber can be constructed to be moved linearly transverse to its capillary passage.

Preferably the action of placing the cassette in the reading device locates an arm which rotates the sample volume chamber 14 through 90° and thus places the fixed prepared volume of sample directly in the required fluid stream between the eluents and the downstream mixing chamber, separation means and detector.

The preferred embodiment of the chromatography device is for use with blood samples in the analysis of glycated haemoglobin. In this case, the walls of the

capillaries are preferably coated with two compounds, one such as heparin or similar to prevent the blood from clotting and the other such as a mild acid to ensure that the sample reaches a pH suitable for the rapid removal of the labile fraction. In the event that the user delays between placing the blood sample on the well and putting the cassette into the reader then no detrimental effect will result as the sample may be held in the capillary passage for many hours without degrading.

A reader device for use with cassettes of the type illustrated in Figure 1 includes a roller positioned to roll over the surface of the cassette (from left to right in Figure 1) to squeeze the chambers 4, 5, 6 to expel the fluid therefrom. In one embodiment the device for the roller is a spring driven mechanism primed by insertion of the cassette. Thus, as the cassette is pushed in, it will prime the mechanism e.g. a clockwork arrangement, that will perform the squeezing of the reagents via the (at least one) roller. Hence, the squeezing of the reagents may be driven by clockwork or alternatively by any other means. More specifically, the cassette primes the spring and moves the roller to its start position. According to the materials used, it is alternatively possible to use a bar or the like which slides over the elongate chambers.

In the case of cassettes of the type illustrated in Figure 4, the reader device includes a

piston ram for each chamber 4,6. Flow of fluids/reagents is dependent on the rates at which the piston rams extend and varying concentration mixtures may be obtained by independently varying the rates of extension of the piston rams. It is possible to have piston ram mechanisms primed in a similar manner to described above and in a reader for a particular application, the mechanism could provide independently varying rates of extension for each piston ram. However, a reader for wide ranging applications may comprise electrical drives for the piston rams, preferably controlled by micro-processor. The drives themselves may comprise a stepping motor or such like used in conjunction with a suitable mechanism such as a rack and pinion or screw.

Thus either automatically (e.g. once the microprocessor has sensed correct insertion of the cassette) or on pressing a proceed button, the roller is released to squeeze the elongate chambers 4,6 or the piston rams controlled to perform the elution and the microprocessor controls the detection (described below) to analyze the eluent stream.

Upon extending the piston rams or squeezing the chambers 4,6, the sample and reagents are moved along through the mixing chamber 18 and into the separation means 20. The separation means, in this cassette, corresponds to the more normal "column" of previous liquid chromatography

devices and is a section in the eluent flow that is filled with a suitable separating media (silica or polymer etc.), chosen in conjunction with the reagents contained in the elongate chambers 4,6 to obtain the required separation. Separated fractions then flow to the detection path 22, which is also integral with the cassette and is not a separate device (as is the case with normal chromatographic systems). In the illustrated embodiment, the detection path 22 comprises a flow cell which includes windows lining up with a detector in the reader. The flow cell has a fixed path length and a fixed volume such that the optical path length through the passing fluid is also fixed. Preferably, a system for use with haemoglobin will use a detector operating within the visual part of the spectrum. The flow cell may therefore use "windows" fabricated from clear plastic material such as can be used for the rest of the cassette. Alternatively when used with a detector operating in the UV range, non-absorbing windows (e.g. quartz) could be used in the cassette or, in a similar way, the cassette can be modified to cater for fluorescent detection if this is necessary.

Finally, the fluid stream passes to an eluent overflow 24 which is a sponge filled area that simply soaks up the eluent stream to prevent fluid egress. It preferably "mops up" the entire eluent stream during the analysis (about 7ml).

The detector in the body of the reading device measures quantities of the sample separated from the separation means. In the preferred embodiment, the detector is required to provide accurate measurement of small amounts of haemoglobin and preferably comprises a high intensity source of radiation between 400 and 430 nanometres with the resulting light signal, after passage through a narrow band width interference filter or similar, having a peak response at 415 nanometres. This light is projected through the flow cell and is measured by a suitable photosensitive diode.

The normal source of light has been in the past a tungsten filament lamp. The preferred hand held device should be battery powered and, in order to minimize power consumption, uses a pulsed light source, preferably a xenon tube. This uses considerably less power than the normal light source of a tungsten filament lamp with constant illumination, but the use of a pulsed source has problems in that successive pulses may be of different intensity. By incorporating a microprocessor, the firing of the xenon tube can be controlled to be at regular intervals and, satisfactory results may be obtained. Using the microprocessor, the signal arriving at the photodiodes through the interference filter and the flow cell is monitored and the peak value is recorded and stored. To further improve results, it is preferred to use a second

photodiode for recording the level of intensity of the same pulse of light through the interference filter and the cassette plastic, but not the blood sample. The difference between the two values obtained from the photodetectors gives a measure of the amount of blood sample in the flow cell but removes the problems of variation of light intensity of successive pulses.

The use of a xenon tube is particularly advantageous in that it has a very large band width and produces not only visible light but ultra violet too. This allows the reader to have wider application since it can be used with cassettes requiring differing frequency light sources.

Although the reader and cassette have been described when used with a flow cell, it is also contemplated that other forms of detection might be used in measuring the sample flow. Further, the actual detector or transducer may be provided on the cassette together with connectors such as studs by which the measurement electronics of the reader may make a connection.

In operation, a blood sample may be placed in the sample well 10, as described above, and then the cassette may be placed in the body of the reading device which then, possibly only with the need to press a proceed button, performs the elution, analysis and calculation of the results without further operator intervention. It is

thus highly convenient and can be used by relatively unskilled persons.

The reading device operates to analyze the results of the photodetector in view of the concentrations used in the eluent stream so as to give an indication of the quantities of different fractions present in the sample. This data be stored for subsequent display or printing or alternatively displayed by way of, for instance, a liquid crystal display. Further the reading device may contain many different processing abilities (programs) for use with different cassettes performing different tests.

Hence, the system allows a doctor to have a reader and a supply of disposable cassettes which can be easily carried around in, for instance, a brief case. Each cassette is preferably designed for a specific test, is used once before disposal and is relatively inexpensive. The disposable nature of the cassettes allows a doctor to perform a wide variety of tests on different people, easily, quickly and without the need for flushing and cleaning the system. Further, the apparatus requires very little skill to operate and a patient may have a reader and a supply of cassettes such that he can make regular tests on himself without any need for him to visit a clinic.

C L A I M S

1. A hand-held chromatography device comprising a reader device and a chromatography cassette for separating, with a varying concentration buffer, fractions of a sample on a binding material and determining the relative quantities of the fractions in the sample, said chromatography cassette being mountable with said reader device and comprising:

a chromatography separation means (20) containing a binding material for binding a sample;

a sample induction means (10,12,14) connected to said chromatography separation means (20) for providing a sample, supplied by a user, to said chromatography separation means (20);

a mixing apparatus (4,6,7,8), connected to said chromatography separation means (20) for producing a flow of varying concentration buffer therethrough; and

a detection path (22) downstream of said chromatography separation means (20) at which the flow of a fraction of said sample out of said chromatography separation means (20) can be detected;

said reader device being mountable with one of a plurality of interchangeable chromatography cassettes and having measurement means for measuring quantities of a sample flowing through said detector path and at least one

of means to display and means to store information relating to the results of the detection.

2. A chromatography device according to claim 1 wherein said mixing apparatus comprises a plurality of elongate chambers (4,6), each holding a fluid, each being connected at one end (7) to a common path (8) leading to said chromatography separation means (20), each being open at the other end, and each having a respective plug (26) sealing with the inner surface of a respective elongate chamber (4,6) so as to hold fluid within the respective elongate chamber (4,6), each plug (26) being moveable lengthwise of the respective elongate chamber (4,6) so as to expel, into the common path (8), the respective fluids from the respective elongate chamber (4,6).

3. A chromatography device according to claim 2 wherein said reader device comprises respective piston rams for moving said plugs (26), the rates of extension of said piston rams in use being controlled by said reader device so as to control the rates at which fluid is expelled from respective elongate chambers (4,6).

4. A chromatography device according to claim 1 wherein said mixing apparatus comprises a plurality of resiliently flexible elongate chambers (4,6), each holding a fluid, each being connected at one end (7) to a common path (8) leading to said chromatography separation means (20) and each having a cross-section which varies along the

length of the elongate chamber (4,6), such that, in use, simultaneously a compression may be formed in each elongate chamber (4,6) to reduce the cross-section of that elongate chamber (4,6) and said compressions may be moved towards respective said one ends so as to expel, into the common path (8), the respective fluids from the elongate chambers (4,6), at rates determined by the cross-sectional area of each elongate chamber (4,6).

5. A chromatography device according to claim 4 wherein said plurality of elongate chambers (4,6) are arranged substantially parallel such that a member, such as a roller, transverse to the elongate chambers, may be used to form each said compression.

6. A chromatography device according to claim 5 wherein said member is mounted on the reader device.

7. A chromatography device according to claim 4, 5 or 6 wherein said plurality of elongate chambers are formed integrally with said cassette structure.

8. A chromatography device according to any one of claims 4 to 7 wherein the cross sectional area of the elongate chambers varies continuously along the length of the elongate chambers.

9. A chromatography device according to any one of claims 4 to 7 wherein the cross sectional area of the elongate chambers varies in discrete steps along the length of the elongate chambers.

10. A reader device according to any one of claims 4 to 9 wherein the action of mounting the reader device with one of said chromatography cassettes, primes a mechanism to provide and move said compressions.

11. A chromatography device according to any preceding claim wherein said sample induction means comprises an inlet tube (10,12) of sufficiently small cross-section to draw by capillary action, directly into a portion (14) of the chromatography cassette a quantity of a sample fluid.

12. A chromatography device according to any preceding claim wherein said sample induction means comprises a sample valve (14) having an aperture therein and being moveable between first and second positions such that, in use, in the first position, a sample fluid may pass through said valve so as to fill the length of the aperture and then, the valve may be moved to the second position so as to provide a sample of known quantity to said chromatography separation means (20).

13. A chromatography device according to claim 12 wherein said second position of said valve (14) is such that the aperture lies in line and between said mixing apparatus (4,6,7,8) and said chromatography separation means (20).

14. A chromatography device according to claim 12 or 13 wherein the action of mounting the reader device with

one of said chromatography cassettes operates a valve mechanism so as to move the valve (14) to said second position.

15. A chromatography device according to any preceding claim wherein the sample induction means is internally coated with at least two compounds for treating the sample.

16. A chromatography device according to any preceding claim wherein said measurement means comprises a pulsed xenon tube light source and a photodetector for measuring attenuation due to out flow of sample fractions from said chromatography separation means (20).

17. A chromatography cassette for use with a reader device according to any one of the preceding claims.

18. A control chromatography cassette for use with a reader device according to any one of claims 1 to 16, said control chromatography cassette comprising:

a sample of known composition;

a chromatography separation means containing a binding material for binding the sample;

a mixing apparatus (4,6,7,8), connected to said chromatography separation means (20) for producing a flow of varying concentration buffer therethrough; and

a detection path (22) downstream of said chromatography separation means (20) at which the flow of a

fraction of said sample out of said chromatography separation means (20) can be deleted.

19. A mixing apparatus for mixing a plurality of fluids to a varying relative concentration, said apparatus comprising a plurality of resiliently flexible elongate chambers (4,6), each holding one of said fluids, each being connected at one end (7) to a common path (8), and each having a cross-section which varies along the length of the elongate chamber (4,6), such that, in use, simultaneously a compression may be formed in each elongate chamber (4,6) to reduce the cross-section of that elongate chamber (4,6) and said compressions may be moved towards respective said one ends (7) so as to expel, into the common path (8), the respective fluids from the elongate chambers (4,6) at rates determined by the cross-sectional area of each elongate chamber (4,6).

20. A sample analysis apparatus having a sample induction means comprising an inlet tube (10,12) of sufficiently small cross-section to draw by capillary action, directly into a portion (14) of the sample analysis apparatus a quantity of a sample fluid.

21. A sample analysis apparatus according to claim 20 wherein said sample induction means comprises a sample valve (14) having an aperture therein and being moveable between first and second positions such that, in use, in the first position, a sample fluid may pass through said

valve so as to fill the length of the aperture and then, the valve may be moved to the second position so as to provide a sample of known quantity to said sample analysis apparatus.

22. A sample analysis apparatus according to claim 20 or 21 wherein the sample induction means is internally coated with at least two compounds for treating the sample.

Fig. 1

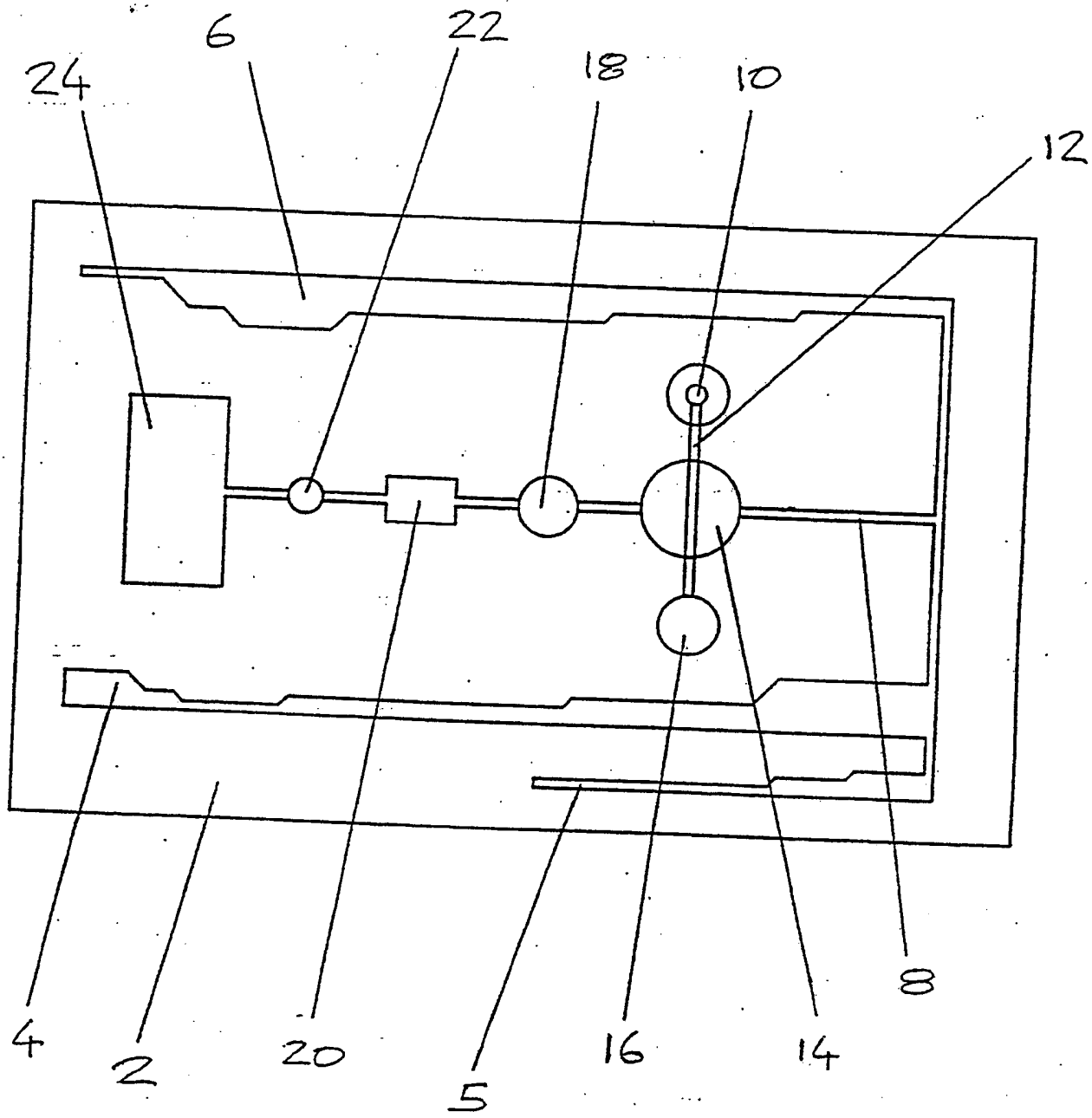


Fig. 2

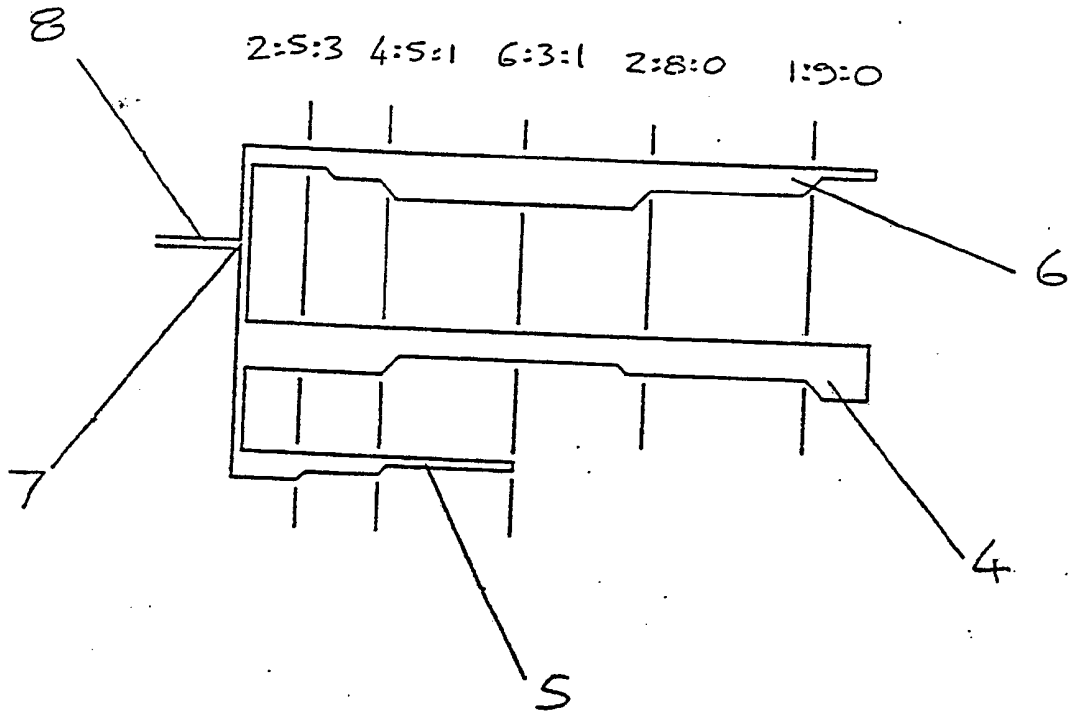


Fig 3(a)

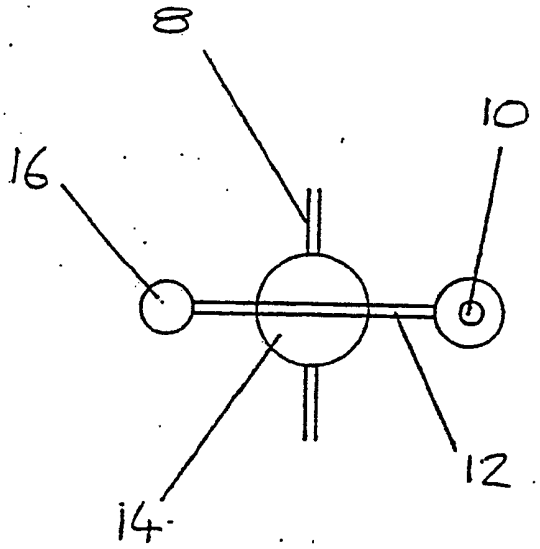


Fig. 3(b)

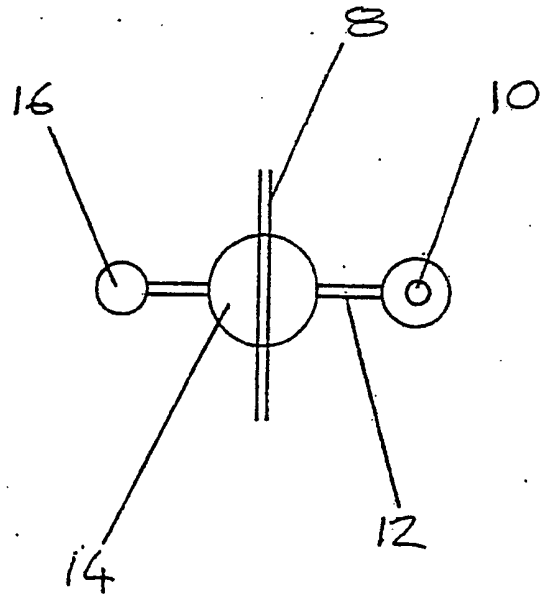
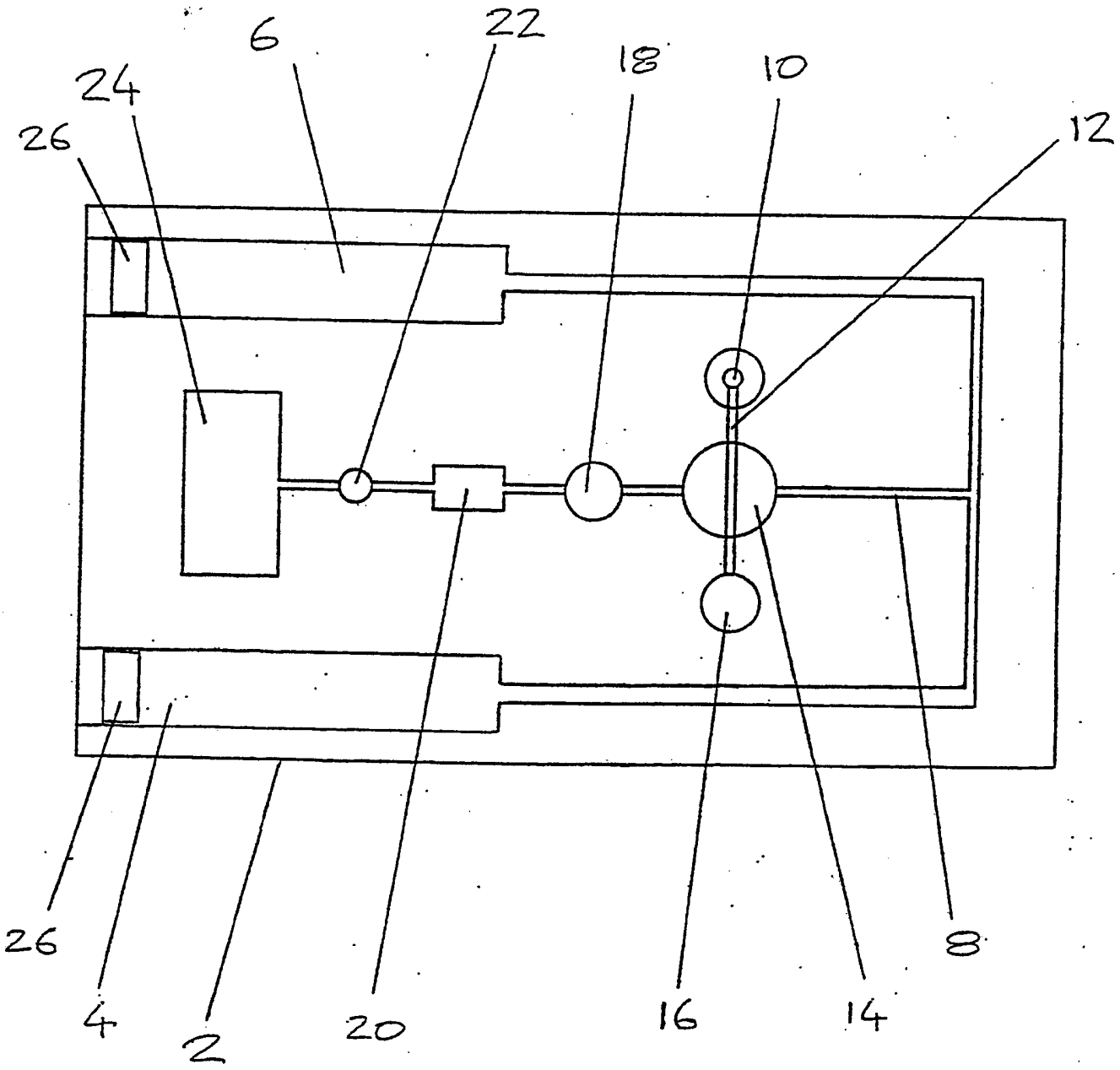


Fig. 4



INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00339

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 G01N30/88; B01L3/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	G01N ; B01L ; B01F

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 381 501 (EASTMAN KODAK) 8 August 1990	19
Y		2,4,5, 7-9
A		3
	see column 12, line 2 - column 13, line 56 see column 18, line 36 - column 19, line 37 see figures 1,2,9	

X	EP,A,0 434 149 (EASTMAN KODAK) 26 June 1991	20,21
Y		12
	see column 3, line 14 - column 4, line 28 see column 5, line 29 - column 6, line 26 see figures	

	-/--	

[10] Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04 JUNE 1993	02.07.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	JOHNSON K.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0 397 424 (BIOTRACK) 14 November 1990	20,22
Y		1,11,15, 17,18
A		7-9,16
	see page 2, line 20 - line 43 see page 3, line 26 - page 4, line 50 see page 7, line 29 - page 8, line 30 see page 10, line 34 - page 11, line 46 see figures 1,3,4	
Y	EP,A,0 307 530 (OTTOSENSORS) 22 March 1989	1,2,4,5, 7-9,11, 12,15, 17,18
	see column 2, line 10 - column 3, line 28 see column 4, line 33 - line 39 see column 5, line 14 - column 6, line 54 see figures	
A	US,A,4 690 801 (H.B. ANDERSON) 1 September 1987 see column 1, line 31 - line 43 see column 2, line 24 - column 3, line 24 see column 3, line 52 - column 4, line 49 see figures 1,4-6	1-7,10, 12,19,21
A	EP,A,0 306 158 (THORN EMI) 8 March 1989 see column 1, line 47 - column 3, line 8 see figure 1	1,11,17, 20

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9300339 SA 70878

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/06/93
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US-A-4690801	01-09-87	None		
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		US-A-	5064618	12-11-91